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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/047,693	01/09/2002	Istvan Bakondi-Kovacs	2664/47002	5182

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KENYON & KENYON
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER

MARX, IRENE

ART UNIT	PAPER NUMBER
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1651

DATE MAILED: 09/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/047,693

Applicant(s)

BAKONDI-KOVACS ET AL.

Examiner

Irene Marx

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 August 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-27 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-27 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

The application should be reviewed for errors. To facilitate processing of papers at the U.S. Patent and Trademark Office, it is recommended that the Application Serial Number be inserted on every page of claims and/or of amendments filed.

The amendment filed 8/22/05 is acknowledged.

Claims 1-27 are being considered on the merits.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-27 are/remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ott *et al.* (GB2,114,978) taken with Tomita *et al.*, Vanek *et al.*, BG 50996 and McIntyre *et al.* for the reasons as stated in the last Office action and the further reasons below.

Response to Arguments

Applicant's arguments have been fully considered but they are not deemed to be persuasive.

Applicants argue that the secondary references are not directed to the production of tobramycin. However, "[n]on-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references." in re Merck & Co., Inc., 800 F.2d 1091, 1097, 231 USPQ 375, 380 (Fed. Cir. 1986). The test of obviousness is "whether the teachings of the prior art, taken as a whole, would have made obvious the claimed invention." In re Gorman, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991).

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The examiner relies on Ott *et al.* and Tomita *et al.* for the disclosure of the production of tobramycin. The deficiencies argued by applicants in the secondary references fail to recognize that Ott *et al.* and Tomita *et al.* are relied on for these teachings. The secondary references are relied on only for their disclosure of the knowledge in the art of the use of regulating constant levels of assimilable carbon and nitrogen sources. The process as claimed is not directed with any specificity to the level at which the "constant levels" are maintained, to the actual carbon source, to the actual nitrogen source or to the strain to be cultured under these conditions to obtain tobramycin. Therefore, the significance of this step cannot be readily assessed. There is no clear correlation between the broad ranges that are claim designated and the results demonstrated in the as-file specification where the nitrogen source, for example, comprises at least soya bean meal, acidic casein, ammonium chloride and cobalt nitrate. It is noted that there is no clear indication that the level of these assimilable nitrogen sources are maintained constant. The references to NH₃-N content are noted, but this examples suggest that the nitrogen is totally depleted rather than maintained "constant".

Applicant argues that McIntyre *et al.* indicates that that the physiological regulation and control of the production of antibiotics in *Streptomyces* is poorly understood (see p. 412, right column, the first sentence of the first full paragraph. However, there is nothing in the instant specification to cure this alleged deficiency. Applicants have not demonstrated on this record that the production of tobramycin by any strain of *Streptomyces* can be improved by the method as claimed. Applicants have cultured two very specific strains of *S. tenebrarius* to obtain favorable results under very specific conditions.

Regarding nitrogen concentration, McIntyre states at page 415, last paragraph that "growth had ceased due to nitrogen limitation" which strongly suggests that the feeding of nitrogen would be appropriate. Regarding the Bulgarian patent cited at page 14, paragraph 2 of the instant Specification, applicant did not discuss this documents, as noted in the last Office action if applicants are in possession of a translation of this document, a copy thereof would be appreciated.

It is also of interest to emphasize once more that the invention as claimed does not stipulate the level at which the constant level is adjusted, except in dependent claims and never for specific carbon and nitrogen sources simultaneously for a specific strain. Moreover, the

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timing or length of the “constant” period are not claim designated. One of ordinary skill in the art would have reasonably expected regulation at constant levels at least at some point during the fermentation, such as at the time of depletion of nutrients.

Regarding arguments that an “improved” yield is required, there is no clear claim designated limitation as to the level of improvement intended. Thus, this functional limitation includes infinitesimal “improvement in yield” and fails to add structure and significantly limit the claim.

In addition, and more importantly, the touted results argued at page 12 of the Response, wherein examples 4-5 are compared to examples 1-3, are not reflected in the claims of record. It is noted that the conditions to obtain any improvement in yield of tobramycin in the instant specification as filed require very specific process parameters. The cultivation requires constant regulation only after the 24th hour, wherein the culture is “fed”, and a medium of specific and defined composition is added to specific strains *S. tenebrarius* NCAIM B(P) 000169 or NCAIM B(P) 000204. From the present record, there is no clear assurance that these strains are freely available to the public or that the results provided can be extrapolated to any microorganism or to any strain of *S. tenebrarius*. The effects of constant feeding at very low or at very high levels of carbon and nitrogen sources on tobramycin production with any microorganism cannot be readily assessed, particularly in view of applicant’s acknowledgement of the unpredictability of the antibiotic production by *Streptomyces*. Applicant did not respond to the query regarding the public availability of the strains of *S. tenebrarius* cultured. IT is noted that the strains are deposited. However, assurances are required in the form of a declaration or evidence such as a current catalogue listing the strains and indicating their availability.

In the process exemplified in Examples 4 and 5 of the specification specific strains and a specific nutrient medium at a specific pH having specific carbon sources are cultured for specific cultivation periods, such as 18 hours. In addition, cultivation parameters include feeding done at the 24th hour; use of 50% sodium glutamate solution and 50% glucose solution. Phosphate content of the glucose solution was in the range of about 0.05 to about 0.2%. Feeding of these solutions were carried out from the 24th hour of the fermentation till the end by controlling in the production phase the glucose and glutamate content in the range of about 0.001 to about 0.05% and about 0.001 to about 0.1%, respectively. Additionally to the above concentrations, ammonia

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solution was also fed in order to control the ammonia nitrogen content in the range of about 30 to about 200 mg/100mL (i.e., about 0.03 to about 0.2%). None of these parameters are claim designated. It is noted that the specification emphasizes that the fed-batch technology used requires that the glucose, glutamate and ammonia nitrogen be regulated. See, e.g., page 13, paragraph 6.

The scope of the showing must be commensurate with the scope of claims to consider evidence probative of unexpected results, for example. In *re* Dill, 202 USPQ 805 (CCPA, 1979), In *re* Lindner 173 USPQ 356 (CCPA 1972), In *re* Hyson, 172 USPQ 399 (CCPA 1972), In *re* Boesch, 205 USPQ 215, (CCPA 1980), In *re* Grasselli, 218 USPQ 769 (Fed. Cir. 1983), In *re* Clemens, 206 USPQ 289 (CCPA 1980). It should be clear that the probative value of the data is not commensurate in scope with the degree of protection sought by the claim.

Therefore the rejection is deemed proper and it is adhered to.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Irene Marx whose telephone number is (571) 272-0919. The examiner can normally be reached on M-F (6:30-3:00).

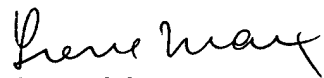
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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A handwritten signature in black ink, appearing to read "Irene Marx". The signature is fluid and cursive, with the first name "Irene" and last name "Marx" clearly distinguishable.

Irene Marx
Primary Examiner
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